CLAIMS

WHAT IS CLAIMED IS:

1. A method of identifying a compound that modulates nuclear receptor activity, said method comprising:

modeling test compounds that fit spatially into a nuclear receptor ligand binding domain of interest using an atomic structural model of the estrogen receptor α ligand binding domain or portion thereof,

screening said test compounds in an assay characterized by binding of a test compound to the ligand binding domain, and

identifying a test compound that modulates nuclear receptor activity, wherein said atomic structural model comprises atomic coordinates of amino acid residues corresponding to residues of human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528.

2. The method of Claim 1 wherein the amino acid residues correspond to residues Met343, Met421, His524, Leu525 and Met528.

3. The method of Claim 1 wherein the test compound is an agonist and nuclear receptor activity is measured by binding of a coactivator to the coactivator binding site.

4. The method of Claim 1 wherein the test compound is an antagonist and nuclear receptor activity is measured by the unwinding of helix 12.

5. The method of Claim 1 wherein the test compound is an antagonist and nuclear receptor activity is measured by the blocking of coactivator binding.

6. The method of Claim 1 wherein said screening is *in vitro*.

7. The method of Claim 6 wherein said screening is high throughput screening.

8. The method of Claim 1 wherein said test compound is from a library of compounds.

9. The method of Claim 1 wherein said test compound is a small organic molecule, a peptide, or peptidomimetic.

10. The method of Claim 1 which further comprises the step of providing the atomic coordinates of the estrogen receptor α ligand binding domain or portion thereof to a computerized modeling system, prior to said modeling step.

11. The method of Claim 1 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors,

progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

12. The method of Claim 11 wherein said nuclear receptor is an estrogen receptor.

13. The method of Claim 12 wherein said estrogen receptor is the estrogen receptor α.

14. A method of identifying a compound that modulates ligand binding to a nuclear receptor, said method comprising:

modeling test compounds that fit spacially into a nuclear receptor ligand binding domain of interest using an atomic structural model of the estrogen receptor α ligand binding domain or portion thereof,

screening said test compounds in an assay characterized by binding of a test compound to the binding domain, and

identifying a test compound that modulates ligand binding to said nuclear receptor,

wherein said atomic structural model comprises atomic coordinates of amino acid residues corresponding to residues of human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528.

15. The method of Claim 14 wherein the amino acid residues correspond to residues Met343, Met421, His524, Leu525 and Met528.

16. The method of Claim 14 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

17. The method of Claim 16 wherein said nuclear receptor is an estrogen receptor.

18. The method of Claim 17 wherein said estrogen receptor is the estrogen receptor α.

19. The method of Claim 14 wherein said screening is *in vitro*.

20. The method of Claim 19 wherein said screening is high throughput screening.

21. The method of Claim 14 wherein said test compound is from a library of compounds.

22. The method of Claim 14 wherein said test compound is an agonist or antagonist of ligand binding.

23. The method of Claim 14 wherein said test compound is a small organic molecule, a peptide, or peptidomimetic.

24. A method for identifying an agonist or antagonist of ligand binding to a nuclear receptor, said method comprising the steps of:
providing the atomic coordinates of the estrogen receptor α ligand binding domain or portion thereof to a computerized modeling system, wherein said atomic coordinates are of the amino acid residues corresponding to residues of human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528;
modeling compounds which fit spacially into the ligand binding domain; and
identifying in an assay for nuclear receptor activity a compound which increases or decreases the activity of the nuclear receptor by binding the ligand binding domain of said nuclear receptor, whereby an agonist or antagonist of ligand binding is identified.

25. The method of Claim 24 wherein the amino acid residues correspond to residues Met343, Met421, His524, Leu525 and Met528.

26. The method of Claim 24 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

27. The method of Claim 26 wherein said nuclear receptor is an estrogen receptor.

28. The method of Claim 27 wherein said estrogen receptor is the estrogen receptor α.

29. A method of modulating nuclear receptor activity in a mammal by administering to a mammal in need thereof a sufficient amount of a compound that fits spatially and preferentially into a ligand binding domain of a nuclear receptor of interest, where said compound is designed so as to distort at least one amino acid residue corresponding to residues of human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528.

30. The method of Claim 29 wherein at least one amino acid residue corresponds to residues Met343, Met421, His524, Leu525 and Met528.

31. The method of Claim 29 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

32. The method of Claim 31 wherein said nuclear receptor is an estrogen receptor.

33. The method of Claim 32 wherein said estrogen receptor is the estrogen receptor α.

34. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecular complex of a compound bound to a nuclear receptor ligand binding domain comprising structure coordinates of amino acids corresponding to human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528 or a homologue of said molecular complex, wherein said homologue comprises a ligand binding domain that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

35. The machine-readable data storage medium of Claim 34 wherein the amino acid residues correspond to residues Met343, Met421, His524, Leu525 and Met528.

36. The machine-readable data storage medium of Claim 34 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

37. The machine-readable data storage medium of Claim 36 wherein said nuclear receptor is an estrogen receptor.

38. The machine-readable data storage medium of Claim 37 wherein said estrogen receptor is the estrogen receptor α.

39. The machine-readable data storage medium of Claim 34 wherein said molecular complex is defined by the set of structure coordinates depicted in Appendix 1 or Appendix 2, or a homologue of said molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

40. A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates selected from the group consisting of coordinates depicted in Appendix 1 or Appendix 2; and said

second set of data comprises an X-ray diffraction pattern of a molecule or molecular complex.

41. The machine-readable data storage medium of Claim 40 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

42. The machine-readable data storage medium of Claim 41 wherein said nuclear receptor is an estrogen receptor.

43. The machine-readable data storage medium of Claim 42 wherein said estrogen receptor is the estrogen receptor α.

44. A cocrystal of a nuclear receptor comprising an agonist bound to the ligand binding domain and a molecule bound to the coactivator binding site of the nuclear receptor, wherein said crystal defracts with at least 2.03Å resolution.

45. The cocrystal of Claim 44 wherein said nuclear receptor is the estrogen receptor α.

46. The cocrystal of Claim 45 wherein said estrogen receptor α is human.

47. The cocrystal of Claim 46 wherein said molecule is peptide.

48. The cocrystal of Claim 47 wherein said peptide comprises a NR-box amino acid sequence or derivative thereof.

49. A cocrystal of a nuclear receptor comprising an antagonist bound to the ligand binding domain of the nuclear receptor, wherein said crystal defracts with at least 1.9Å resolution.

50. The cocrystal of Claim 49 wherein said nuclear receptor is the estrogen receptor α.

51. The cocrystal of Claim 50 wherein said estrogen receptor α is human.

52. A computational method of designing a nuclear receptor ligand where at least one amino acid residue of a nuclear receptor LBD that corresponds to human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, interacts with at least one first chemical moiety of said ligand, comprising the step of selecting at least one chemical modification of said first chemical moiety to produce a second chemical moiety with a structure to either decrease or increase an interaction between said interacting amino acid and said second chemical moiety compared to said interaction between said interacting amino acid and said first chemical moiety.

53. The method of Claim 52 wherein at least one amino acid residue corresponds to residues Met343, Met421, His524, Leu525 and Met528.

54. The method of Claim 52 further comprising determining a change in interaction between said interacting amino acid and said ligand after chemical modification of said first chemical moiety.

55. The method of Claim 52 wherein said chemical modification enhances hydrogen bonding interaction, charge interaction, hydrophobic interaction, Van Der Waals interaction or dipole interaction between said second chemical moiety and said interacting amino acid compared to said first chemical moiety and said interacting amino acid.

56. The method of Claim 52 wherein said chemical modification reduces hydrogen bonding interaction, charge interaction, hydrophobic interaction, Van Der Waals interaction or dipole interaction between said second chemical moiety and said interacting amino acid compared to said first chemical moiety and said interacting amino acid.

57. The method of Claim 52 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

58. The method of Claim 57 wherein said nuclear receptor is an estrogen receptor.

59. The method of Claim 52 wherein the estrogen receptor is the estrogen receptor α.

60. The method of Claim 59 wherein the ligand is an agonist.

61. The method of Claim 60 wherein the ligand is selected from the group consisting of 17β-estradiol, diethylstilbestrol, moxestrol, mesohexestrol, coumestrol, Δ^9-THC, o,p-DDT, zearalenone and kepone.

62. The method of Claim 61 wherein the ligand is 17β-estradiol, and the first chemical moiety is a free carbon of the A' ring located at a position selected from the group consisting of C6α, C7α, C12α, C15α, C16α and C17α.

63. The method of Claim 59 wherein the ligand is an antagonist.

64. The method of Claim 63 wherein the ligand is selected from the group consisting of ICI 164,384 and EM800.

65. The method of Claim 59 wherein the ligand is a selective estrogen receptor modulator.

66. The method of Claim 65 wherein the ligand is selected from the group consisting of tamoxifen, raloxifene and GW5638.

67. A method of modulating nuclear receptor activity in a mammal by administering to a mammal in need thereof a sufficient amount of a ligand that fits spatially and preferentially into a ligand binding domain of a nuclear receptor of interest, wherein said ligand is designed by a computational method where at least one amino acid residue of a nuclear receptor ligand binding domain that corresponds to human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, interacts with at least one first chemical moiety of said ligand, comprising the step of selecting at least one chemical modification of said first chemical moiety to produce a second chemical moiety with a structure to either decrease or increase an interaction between said interacting amino acid and said second chemical moiety compared to said interaction between said interacting amino acid and said first chemical moiety.

68. The method of Claim 67 wherein at least one amino acid residue corresponds to residues Met343, Met421, His524, Leu525 and Met528.

69. The method of Claim 67 wherein said ligand is an antagonist.

70. The method of Claim 67 wherein said ligand is an agonist.

71. The method of Claim 70 which further comprises administering a coactivator mimic designed by a computational method where at least one amino acid residue of a nuclear receptor coactivator binding site that corresponds to human estrogen receptor α helix 3 residues Leu354, Val355, Met357, Ile358, Ala361 and Lys362, helix 4 residue Phe367, helix 5 residues Gln375, Val376, Leu379 and Glu380, helix 6 residue Trp383, and helix 12 residues Asp538, Leu539, Glu542, Met543 and Leu544, interacts with at least one first chemical moiety of said coactivator mimic, comprising the step of selecting at least one chemical modification of said first chemical moiety to produce a second chemical moiety with a structure to either decrease or increase an interaction between said interacting amino acid and said second chemical moiety compared to said interaction between said interacting amino acid and said first chemical moiety.